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EXAMINER

TURNER, SHARON L

ART UNIT PAPER NUMBER

1647

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/897,438

Applicant(s)

MIKOSHIBA ET AL.

Examiner

Sharon L. Turner

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-8, 10 and 11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-8, 10 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8-9-04</u> . | 6) <input type="checkbox"/> Other: _____ |

Response to Amendment

1. The amendment filed 11-10-04 has been entered into the record and has been fully considered.
2. The IDS file 8-9-04 has been considered as indicated on the PTO-1449 but has been crossed off as the reference is not suitable for publication on the face of the patent.
3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.
4. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

Election/Restriction

5. Applicant's election of Group II, claims 4-8 and 10-11 in part in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
6. Claims 1-3 and 9 are canceled. Claims 4-8 and 10-11 are pending.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
8. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 4-5 are presented in new terms. In particular, amended claim 4 is drawn to the new limitations of "a region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2", "a repeat site nor any portion of an F-spondin domain", "of the monoclonal antibody recognition region", and "wherein the polypeptide binds to the monoclonal antibody to Reelin protein that binds to SEQ ID NO:2".

However, the specification does not support the newly generic recitation of polypeptide defined by recognition by a monoclonal antibody that binds SEQ ID NO:2. The previous language and language supported by the specification denot a particular CR-50 antibody of the prior art, yet the new recitation is deemed to improperly broaden, as the peptide encompassed may be any that is noted to be capable of binding a antibody that binds SEQ ID NO:2. The species of CR-50 does not support the newly recited genus of peptides so encompassed.

Moreover, while the specification provides for the recitation of neither a repeat site nor a F-spondin domain, the exclusion does not appear to be supported as to the new exclusion of peptides not comprising any portion of an F-spondin domain. Claim 5 is newly directed to polynucleotides containing neither a nucleotide sequence encoding a repeat domain nor a nucleotide sequence encoding any portion of an F-spondin domain and that encodes a polypeptide that binds to a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2.

Again, the species of CR-50 antibody does not support the newly defined polynucleotides or polypeptides that bind a monoclonal antibody that binds SEQ ID NO:2 nor the exclusion of any portion of an F-spondin domain. Thus, the noted recitations constitute new matter.

Claims 4-8 and 10-11 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes a polypeptide sequence consisting of SEQ ID NO:2. However, the claims as newly written are directed to polynucleotides "encoding polypeptides selected from (a) a polypeptide comprising a region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2 and containing neither a repeat site nor any portion of an F-sponding domain, wherein the polypeptide is derived from a mouse Reelin polypeptide, (b) a polypeptide comprising an amino acid sequence shown in SEQ ID NO:2 and containing neither a repeat site nor any portion of an F-spondin domain, (c) the polypeptide of a or b comprising a deletion substitution or addition of one or more amino acid(s) of the monoclonal antibody recognition region; and (d) a polypeptide encoded by a degenerative nucleic acid sequence of the polypeptides of any of a to c and wherein the polypeptide binds the monoclonal antibody to Reelin protein that binds to SEQ ID NO:2; as well as polynucleotides as similarly defined in claim 5 denoting polynucleotides containing neither a nucleotide sequence encoding a repeat domain nor a nucleotide sequence encoding any portion of an F-spondin domain and that encodes a polypeptide that binds to a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2.

Again, the species of CR-50 antibody does not support the newly defined polynucleotides or polypeptides that bind a monoclonal antibody that binds SEQ ID NO:2 nor the exclusion of any portion of an F-spondin domain.

Antibody binding is a property which depends upon the antibody to be tested. However, here the antibody is only defined by its ability to bind a peptide having SEQ ID NO:2, a circular definition which does not direct to those elements or sequences that may be included or varied such that binding still occurs to any portion thereof. Moreover, the claims do not define the amino acids of the monoclonal antibody recognition region. Such regions generally include merely 5-6 amino acid stretches, yet the specification fails to delineate which amino acids constitute the recognition region nor which should be conserved or excluded from the genus claimed. Hence the specification fails to describe or evidence possession of those members that fall under the genus recitation defined via functional binding but for which no structural guidance is provided.

Similarly to the encoding nucleic acids, encoding sequences may bear little to no structural or functional characteristics amongst those peptides they encode. Moreover, the structural requirements of the claims are inclusive of unlimited variation as encompassed by insertion, substitution or deletion variants and degenerate sequences. Additionally the claims recite compositions that stimulate the assembly of Reelin protein and that are useful for diagnosis and/or treatment of diseases resulting from abnormally positioned neurons which comprise the aforementioned nucleic acids.

However, the instant disclosure of a single polypeptide, that of SEQ ID NO:2, and a single nucleic acid encoding it (SEQ ID NO:1) does not adequately support the scope of the

claimed genus, which encompasses a substantial variety of genera and subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention”. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) (“[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.”) Thus, an applicant complies with the written description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the ‘525 patent, “requires a precise definition, such as by structure, formula, chemical name, or physical properties,” not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, “an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself.” Id at 1170, 25 USPQ2d at 1606.”

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence encoding the polypeptide sequence SEQ ID NO: 2 and no other nucleic acid or amino acid sequences that are proposed to correspond to the same structural and/or

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functional characteristics. While the specification does note certain functional recitations, for example the ability to bind, the specification fails to delineate by structure those molecules that exhibit the noted function. However, the ability to bind is an unpredictable characteristic as previously noted in Skolnick and Jobling of record. Given the fact that the specification fails to provide objective evidence of any additional sequences that are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim.

9. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:1, does not reasonably provide enablement for polynucleotides encoding polypeptides comprising a region recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO:2 and containing neither a repeat site nor any portion of an F-sponding domain, as claimed with unlimited deletions, substitutions or additions as encompassed by degenerative sequences and the functional limitation of binding a monoclonal antibody that binds SEQ ID NO:2, that stimulate the assembly of Reelin protein and that are useful for diagnosis and/or treatment of diseases resulting from abnormally positioned neurons comprised of the aforementioned nucleic and/or amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include

the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. Thus, these references exemplify the importance of conserved structural components to both biological function and immunological recognition. The skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted and that variations in sequence may effect such structure and immunological recognition.

Instant specification discloses a CR-50 epitope designated as SEQ ID NO:2, corresponding to residues 230-346 of Reelin protein, see in particular p. 4, lines 11-18. However, the claims are drawn generically to polynucleotides encoding polypeptides comprising a CR-50 antibody recognition site of Reelin protein and neither a F-spondin domain nor a repeat site, comprising SEQ ID NO:2 and neither a F-spondin domain nor a repeat site, polypeptides as above comprising a deletion, substitution or addition of one or more amino acids, polypeptides encoded by degenerative nucleic acids and wherein the polypeptide binds to antibody CR-50. Additionally the claims recite compositions that stimulate the assembly of Reelin protein and

that are useful for diagnosis and/or treatment of diseases resulting from abnormally positioned neurons which comprise the aforementioned nucleic acids.

Thus, the claims are directed to polynucleotides encoding peptides with greater than single amino acid substitutions, deletions and insertions and to partial peptide fragments which bind an antibody that binds SEQ ID NO:2. Yet the specification fails to teach alternative sequences other than SEQ ID NO:2 encoded by SEQ ID NO:1 and degenerate sequences thereof, capable of binding such antibody that corresponds to the claim recitations. There is no disclosure of those residues which may be replaced, modified, inserted or deleted without abrogating the disclosed immunological reactivity. The functional recitation of binding is delimited only via that function, yet the specification does not teach the structural modifications encompassed while retaining function and the claim are therefore essentially unlimited in structure. Binding may be affected by merely 5-6 amino acid stretches. Yet the claims do not define the recognition region required and the antibodies that may be made to the different epitopes are essentially unlimited in structure, ie., multiple antibodies may be generated and suitably screened. Moreover, as pertinent in claims 10-11, the specification fails to teach such suitable compositions for stimulating the assembly of Reelin protein molecules or for providing a pharmaceutical for diagnosis or treatment of diseases resulting from abnormally positioned neurons.

At most the specification recognizes an epitope region which binds a CR-50 antibody and which spontaneously forms a regular homopolymer via electrostatic interaction as disclosed at p. 4, lines 11-18. Furthermore, Reelin mutants are only recognized in mice and the model system is pertinent only to the Reelin phenotype which does not approximate all recognized abnormally

positioned neurons but only those recognized as aberrantly positioned in Reelin animals, see for example Curran et al., Br. Res. & Br. Res. Reviews, 26(2-3):285-94, May 1998.

The specification does not enable the broad scope of the claims that encompass a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke immune responses or to provide for the required effects. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not expect functional conservation or immunological recognition among homologous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The artisan recognizes that such structure is critical to antibody binding. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments encompassed by the claims, one skilled in the art would be forced into undue experimentation in order to determine those peptides which correlate to the recitations of the claims, i.e., to define those residues capable of CR-50 monoclonal antibody binding, stimulating the assembly of Reelin proteins or diagnosing or treating diseases associated with abnormally positioned neurons.

Further the artisan would be required to confirm the peptides utility in the process of making and using a polypeptide capable of stimulating an antibody capable of binding reelin products, thus inhibiting Reelin function, see in particular Utsunomiya-Tate N., et al., PNAS, 97(17):9729-34, Aug. 15, 2000. Therefore, the enablement provided by the specification, in view of the skill in the art, is not commensurate in scope with the claims.

The ability to “make and test” is not the standard for an enabling disclosure. The instant specification fails to identify that structure which is required for the claimed biological . Moreover the activity of stimulating the assembly of a Reelin protein molecule, is not limited to mouse Reelin or to anti-Reelin antibody binding activity to which applicants refer within the specification. Neither are the diseases capable of diagnosis and/or treatment referenced by the claim as the specification suggests. The limitations of the specification cannot be read into the claims but must be recited thereby.

In the absence of guidance, a practitioner of the art of molecular biology would have to resort to a substantial amount of experimental trial and error to produce the peptides as claimed. This trial and error would constitute undue experimentation as there is no guidance as to which of the modifications would reasonably correspond to the structures and/or functions of the claims and therefore, the instant specification is not enabling for the full scope of the peptides claimed. The standard for an enabling disclosure is not one of making and testing and the claims constitute a “wish to know”. Because there is no reasonable expectation that any modification would either correspond both structurally and functionally, the experimentation is undue.

What is required is some degree of predictability as to those modifications that are appropriate. The instant specification fails to provide the requisite elements and thus one is not provided any expectation of antibody binding.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by de Bergeyck et al., J. of Neurosci. Methods, 82:17-24, 1998.

DeBergeyck et al., teach peptides useful in the generation of various antibodies to the mouse Reeler peptide. As in the abstract,

"Reelin, the extracellular matrix protein defective in reeler mutant mice, plays a key role during brain development. We therefore raised antibodies directed against various reelin epitopes in order to facilitate biochemical and cell biological studies of this important molecule. Homozygous reeler mice with a large deletion of most of the reelin gene were immunized with

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fusion proteins and carrier-coupled peptides corresponding to parts of the reelin sequence. Monoclonal antibodies were produced using classical procedures, screened using ELISA and/or western blot prepared with the antigen, and tested by immunohistochemistry and immunoprecipitation assays to detect endogenous reelin. The labeling of Cajal–Retzius cells in the embryonic mouse telencephalon was selected as criterion for positivity in immunohistochemistry. A total of 11 monoclonal antibodies were obtained, providing useful additions to the widely used antibody CR-50. Five are directed against the N-terminal part of reelin, among which three recognize the region that has significant similarity with F-spondin, and two are specific for hinge region located downstream from the F-spondin similarity region and upstream from the reelin repeats. Six antibodies are directed against the C-terminal part of reelin, among which one anti-peptide antibody recognizes the highly basic C-terminal segment. Antibodies against the N-terminal region stain well in immunohistochemistry. By comparison, the labeling of embryonic Cajal–Retzius cells with antibodies directed against the C-terminal region is weaker, suggesting that this part of the molecule might be modified or not be as readily accessible in the tissue as the N-terminus."

In particular, the peptide immunogens are represented as in Figure 1B p. 18. Applicant's specification notes that the CR-50 recognition site is within residues 230-346 of Reelin. Peptide H164-496 is noted to be deleted in both the F-spondin region as well as the C-terminal repeat region domains. As the peptide comprises residues 230-346, comprising the CR-50 epitope region, it would bind the CR-50 antibody, an antibody that binds SEQ ID NO:2 as the structure is so defined in the specification. The polynucleotides encoding the same residues shares identity and/or similarity to SEQ ID NO:1. Further the reference teaches analysis of the antibody specificity using peptides 164-405, 164-371 and 164-245, see in particular p. 22, columns 1-2, 3.3. *Anti-protein H*. Thus, the polynucleotides encoding the peptide fragments anticipate the claimed compositions.

Applicants argue in the response of 3-01-04 that the art does not meet the claim limitations in that the H164-496 peptide is only missing a portion of the F-spondin domain.

Applicants arguments have been fully considered but are not persuasive. Applicant's concede that the F-spondin region corresponds to amino acids 28-190 of Reelin. While it is agreed that the H164-496 peptide only comprises a portion (27 amino acids) of the F-spondin

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domain, such does not correspond to having an F-spondin domain. Moreover, the claims are directed to deletion, substitution and addition mutants. At the very least the H164-496 mutant may correspond to such recitations. The peptide does not comprise a F-spondin domain because the domain is not included in full and the mutant may further correspond to a mutant lacking any of an F-spondin domain while containing a 27 amino acid addition. While the new limitations of claims 4-5 denote that no portion may be of the F-spondin domain, the claim allows for structural variability inclusive of additions or one or more amino acids of the monoclonal antibody recognition region and degenerative sequences. Accordingly, the noted structure would apparently be inclusive as claimed and therefore rejection is maintained on these grounds. The structural variability encompassed is inclusive of portions of a F-spondin domain.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Bergeyck et al., J. of Neurosci. Methods, 82:17-24, 1998, Nakajima et al., PNAS 94:8196-201, July 1997 and Miyata et al., J. of Neurosci., 17(10):3599-3609, 1997.

de Bergeyck et al., teach as set forth above. In particular, DeBergeyck et al., teach peptides useful in the generation of various antibodies to different portions of the mouse Reeler peptide for the purpose of providing diagnostic reagents with the advantage of binding specific regions of the molecule to aid in deciphering the function of the different portions of the peptide within the host. De Bergeyck et al., teach peptides comprising the CR-50 region as useful for the stimulation of antibodies reactive thereto. The H164-496 comprises the CR-50 domain but lacks a full F-spondin domain and lacks any portion of the repeats.

de Bergeyck et al., does not teach a specific peptide immunogen consisting of the CR-50 epitope region and thus containing none of the F-spondin domain and none of the repeat site. However, de Bergeyck et al., notes the desire to generate various antibodies specific to different portions of the mouse Reeler peptide for the purpose of providing diagnostic reagents with the advantage of binding specific regions of the molecule to aid in deciphering the function of the different portions of the peptide within the host. The reference also teaches testing with peptides of residues 164-405, 164-371 and 164-245.

Nakajima et al., teach antibody CR-50 generated via immunization with homogenates of normal embryonic brain, see in particular abstract. Nakajima notes that it is still unclear whether Reelin, especially the CR-50 epitope region is indeed responsible for the reeler phenotype in vivo. However, Nakajima notes that injection of the antibody in the embryonic stage is capable of disrupting the normal pattern of development in the embryo converting it to the phenotype of

the reeler mutant. Nakajima notes this finding evidences that the CR-50 epitope plays a central role in this function, see in particular abstract.

Miyata et al., teach that the CR-50 antibody regulates Purkinje cell alignment within the CNS in an in vitro model system, see in particular abstract. Further Miyata notes that the study reveals important steps downstream of reelin, see in particular p.3608, column 2, last paragraph. Miyata notes that the in vitro assays are useful for assessment of the scrambler phenotype using the CR-50 antibody. In addition CR-50 is noted to be useful for functional experiments in vivo.

Thus, one of skill in the art would be motivated to produce a peptide consisting of the CR-50 epitope peptide to make CR-50 epitope specific antibodies capable of blocking the noted reeler phenotype as suggested by Nakajima and Miyata. One of skill in the art would expect success using such techniques given the high skill in the art of making antibodies specific to various peptide regions and the teachings of Miyata and Nakajima that it is the CR-50 epitope that directs the reeler phenotype. The antibody so generated would provide for the advantages of CR-50 in functional testing within the in vitro and in vivo model systems while containing neither a F-spondin domain nor repeat site. Thus, the cumulative reference teaching render the claimed invention obvious to one of skill in the art.

Status of Claims

15. No claims are allowed.
16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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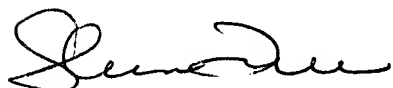
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.



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February 21, 2005

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PATENT EXAMINER